CNS Drug Reviews
Vol. 7, No. 4, pp. 399–414

SCH 23390: The First Selective Dopamine D_1-Like Receptor Antagonist

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Key Words: Dopamine—Dopamine D_1 receptors—Epileptiform activity—Neurological disorders—SCH 23390.

ABSTRACT

SCH 23390, the halobenzazepine (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine, is a highly potent and selective dopamine D_1-like receptor antagonist with a K_i of 0.2 and 0.3 nM for the D_1 and D_5 dopamine receptor subtypes, respectively. *In vitro*, it also binds with high affinity to the 5-HT_2 and 5-HT_{1C} serotonin receptor subtypes. However, the doses required to induce a similar response *in vivo* are greater than 10-fold higher than those required to induce a D_1-mediated response.

Previous *in vivo* pharmacological studies with SCH 23390 have shown it to abolish generalized seizures evoked by the chemoconvulsants: pilocarpine and soman. These studies provide evidence of the potential importance of D_1-like dopaminergic receptor mechanisms in facilitating the initiation and spread of seizures. The inference from a majority of studies is that the activation of dopamine D_1 receptors facilitates seizure activity, whereas activation of D_2 receptors may inhibit the development of seizures. SCH 23390 has also been used in studies of other neurological disorders in which the dopamine system has been implicated, such as psychosis and Parkinson's disease. Apart from the study of neurological disorders, SCH 23390 has been extensively used as a tool in the topographical determination of brain D_1 receptors in rodents, nonhuman primates, and humans.

In summary, SCH 23390 has been a major tool in gaining a better understanding of the role of the dopamine system, more specifically the D_1 receptor, in neurological function and dysfunction.

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INTRODUCTION

Dopamine receptors have been associated with many neurological disorders, including most notably Parkinson's disease and schizophrenia. Pharmacological studies carried out before the advent of receptor cloning techniques supported the existence of just two dopamine receptors, termed D_1 and D_2, based on their positive and negative coupling to adenylate cyclase, mediated by a G-protein and effector (45). For example, D_1 receptor activation enhances cAMP formation, whereas activation of D_2 receptors inhibits cAMP formation. However, it was not until the 1980s that cloning studies revealed that there are at least five receptors, which have been termed D_1–D_5. The cloning of the D_2 splice variants (D_{2L} and D_{2S}) was followed by the cloning of products of different genes, such as the D_3 (60), D_4 (68), and D_5 receptors (64). These receptor subtypes were then assigned to either the D_1-like subfamily (which includes the D_1 and D_5 receptors) or D_2-like subfamily (which includes the D_2, D_3, and D_4 receptors), depending on their coupling to adenylate cyclase. Analysis of the amino acid sequences of the dopamine receptor subtypes reveals that there is a high degree of homology between the members of the subfamilies (43). The genomic organization of the dopamine receptors also supports the notion that they derive from the divergence of two gene subfamilies (49).

The D_1-like receptor proteins, similar to the D_2-like receptors, contain seven hydrophobic alpha-helical transmembrane spanning segments linked to more hydrophilic segments with an extracellular amino terminus. This is the classical conformation for G-protein-coupled receptors (28).

D_1 receptors are found in high levels in the dopamine rich areas of the brain, such as the caudate nucleus, putamen, substantia nigra, nucleus accumbens, hypothalamus, thalamus, frontal cortex, and olfactory tubercle, whereas the D_5 receptor is present, although at a low concentrations, in the hippocampus, thalamus, lateral mammillary nucleus, and cerebral cortex (35). Both of these receptor subtypes are capable of stimulating adenylyl cyclase (65). Gene transcripts of D_3, D_4, and D_5 receptors are much less abundant and display more discrete expression in the brain than those of the D_1 (59). In contrast, those of D_1 and D_2 are virtually absent from the dorsal striatum, which are only expressed in certain limbic regions (e.g., hippocampus). A consistent difference between the D_1 and D_5 receptors is that dopamine is approximately 10 times more potent at the D_5 receptor (Table 1). The function of the D_5 receptor is not understood but the D_1 receptor seems to mediate important central nervous system (CNS) actions of dopamine to control movement (17) and cognitive function (55).

SCH 23390 is a potent, enantioselective dopamine D_1-like receptor antagonist (11,40,41,53), although *in vivo* studies suggest that SCH 23390 may also have a moderately high affinity for the 5-HT_2 and 5-HT_{1C} receptors (12). The affinity of ligands at dopamine receptors is summarized in Table 1. SCH 23390 is a very short-acting compound with an elimination half-life of around 25 min following administration of 0.3 mg/kg i.p. in the rat (46). The few pharmacokinetic data available suggest that the compound undergoes extensive first-pass metabolism when administered orally (41).

Over the last two decades, our understanding of the function of the dopamine receptor and its neuronal location has been much aided by this drug. For example, it has been a widely used tool in behavioral and radioligand binding studies. In addition, more recent studies have proposed its effectiveness as an anticonvulsant in certain experimental paradigms.

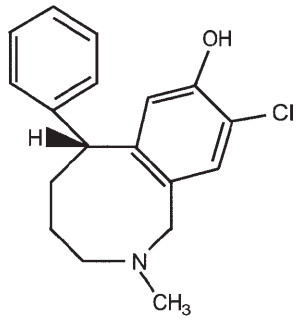

Fig. 1. Chemical structure of SCH 23390, (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

CHEMISTRY

SCH 23390, the 3-methyl, 7-chloro analogue of the D_1 agonist SKF 38393, is a potent enantioselective dopamine D_1-like receptor antagonist. The active enantiomer of the benzazepine ligand ($C_{17}H_{18}ClNO$) is (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Fig. 1), compared with the inactive (S) enantiomer (SCH 23388). The commercially available hydrochloride salt has a molecular weight of 324.25 and is a white solid soluble in water (8 mg/mL), DMSO (3 mg/mL), or ethanol (2 mg/mL). Dopamine D_1-like receptor antagonists are commonly 1-phenyl-3-methyl-7-halogenated- benzazepines. Both the 3-methyl and 7-chloro substituents impart antagonist activity, however, the halogen is also essential (42). Also, an important part of

TABLE 1. Dissociation constants (K_i) for some of the selective/unselective dopamine antagonists/agonists at dopamine receptors

	K_i values (nm)				
	D_1-like		D_2-like		
Ligand	D_1	D_5	D_2	D_3	D_4
Antagonists					
Chlorpromazine	~90	~130	3	4	35
Clozapine	~170	~330	~230	~170	21
Haloperidol	~80	~100	1.2	~7	2.3
SCH 23390	~0.2	0.3	~1100	~800	~3000
S-Sulpiride	~45,000	~77,000	~15	~13	1000
R-Sulpiride	~19,000	29,000	~900	~400	970
Agonists					
(–)-Apomorphine	~0.7		~0.7	~32	~4
Dopamine	0.9	<0.9	~7	~4	~30
7-OH-DPAT	~5000		10	~1	650
SKF 38393	1	~0.5	~150	~5000	~1000

the interaction between the phenyl ring in the benzazepines and the receptor is due to electrostatic forces with the phenyl ring interacting with the same receptor site as the oxygen atom of the 8-hydroxy group (54).

NEUROCHEMISTRY

Studies of changes in brain neurochemistry following the administration of SCH 23390 *in vivo* have focused primarily on the dopamine-rich nuclei, including the caudate, putamen, and accumbens, and have primarily utilized microdialysis (73,74) to monitor changes. In one *in vivo* study, local perfusion (90 min) of SCH 23390 (1 and 10 μM) into the striatum of halothane-anesthetized rats increased extracellular dopamine over basal levels dose dependently, but had no effect on gamma-aminobutyric acid (GABA) and glutamate levels (50). The increase in striatal extracellular dopamine in an anesthetized preparation was not observed following parenteral or intranigral infusion (57,77). However, a dose-dependent increase in striatal extracellular dopamine and its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) was observed by Imperato et al. (1987) in the unanesthetized rat, following doses greater than 0.012 mg/kg (subcutaneous [s.c.]). Tomiyama et al. (66) suggest that the SCH 23390-evoked increase in dopamine and its metabolites is mediated by the reverse operation of the dopamine transporter, and not the D_1 receptor, because of the insensitivity of SCH 23390 to TTX, a sodium-channel blocker. The lack of increase in striatal extracellular GABA from basal levels is probably due to the inhibition of the dopamine D_1 release-enhancing heteroreceptors located on the terminals of the GABAergic interneurons (56). A decrease in acetylcholine and choline was also observed in the rat striatum after infusion of SCH 23390, probably due to a decrease in the release and turnover of acetylcholine, that originate from the striatal cholinergic interneurons (29). When studying the effects of drugs on neurotransmitters in an awake animal, the effect of environmental stress in these and other studies has been shown to alter the extracellular concentration of neurotransmitters in many brain locations. Studies have conclusively linked environmental stress with increases in the levels of dopamine and other neurotransmitters in the brain (27,31).

More recent *in vivo* studies have been directed at the prefrontal cortex (PFC), where the A10 dopaminergic neurons, which originate in the ventral tegmental area, project (6). Perfusion with the D_1 agonist SKF 38393 (2–200 μM), via a dialysis probe into the medial PFC dose-relatedly reduced extracellular concentrations of both glutamate and GABA. The neurochemical changes evoked by 200 μM SKF 38393 were, however, prevented by co-perfusion with SCH 23390 (40 μM). These results suggest that the dopaminergic hyperactivity may lead to the hypofunction of glutamatergic and GABAergic systems in the PFC via D_1 dopamine receptor stimulation (1).

In one *in vitro* study, striatal slices from the rat were preincubated with [^{3}H]GABA and superfused in the presence of nipecotic and aminooxyacetic acids, which are inhibitors of high-affinity GABA transport and GABA aminotransferase, respectively. GABA efflux was estimated by monitoring tritium efflux, 98% of which was in the form of [^{3}H]GABA. The overflow of GABA evoked by electrical field stimulation (8 Hz) was increased twofold by SKF 38393 (10 μM) but was completely blocked by SCH 23390 (10 μM). However, SCH 23390 had no effect on GABA overflow when given alone. Thus, activation of

dopamine D_1 receptors appears to exert an excitatory influence on GABA release; however, this effect was not elicited by endogenous dopamine under the conditions of this experiment (36). Another *in vitro* study examined the effects of SCH 23390 on the spontaneous and calcium-dependent, potassium-induced release of [^{3}H]GABA accumulated by slices of rat substantia nigra. SKF 38393 and dopamine were without effect on [^{3}H]GABA efflux when administered by themselves (1–40 μM) or in the presence of the phosphodiesterase inhibitor isobutylmethylxanthine (IBMX) (0.5 μM), but they potentiated evoked release in the presence of forskolin (0.5 μM), an adenylate cyclase activator (62).

PHARMACOLOGY

Effects on Motor Behavior

The pharmacologic profile of SCH 23390 resembles that of many other neuroleptics, and early studies showed it had an antistereotypic effect in mice, rats, and dogs, as well as a cataleptogenic effect and an inhibitory effect on amphetamine-induced circling in rats (21,22). In rodents, SCH 23390 inhibited motor stimulation induced by apomorphine or by selective D_2 agonists, such as RU 24213. This inhibition is evident across a range of behaviors (26,61), and it has been suggested that SCH 23390 blocks all motor activity (61). This result suggests that there is a definite synergy/cooperation between the D_1 and D_2 receptor subtypes in motor behavior. However, in drug discrimination paradigms SCH 23390 blocked the discriminative stimulus properties of amphetamine but not apomorphine (71), suggesting that the two receptor subtypes can act in a functionally independent manner to regulate response. Studies with SCH 23390 in nociceptive and thermic paradigms have shown that it can reverse the increase in tail flick latency evoked by the D_1 agonist SKF 38393, following long-term treatment with haloperidol (9).

More recently studies with SCH 23390 have focused on understanding the role of the basal ganglia in motor behavior to gain a better insight into the role of specific dopamine receptors in diseases such as idiopathic parkinsonism. The role of dopamine in the subthalamic nucleus to control motor behavior was investigated in rats using bilateral microinfusions of SCH 23390, which induced catalepsy. These findings suggest that dopamine D_1 receptors within the subthalamic nucleus (STN) play an important role in the regulation of motor functions (38). In the globus pallidus (GP) of rats bilateral microinfusions of SCH 23390 were used to investigate the role of dopamine receptors in motor control. Results show that SCH 23390 injected into the GP induced akinesia, as determined by means of the catalepsy test. These findings indicate that pallidal dopamine D_1 receptors are critically involved in the control of motor behavior. These findings further imply that defective dopaminergic transmission in the GP and STN might contribute to akinesia due to lesion- or drug-induced dopamine hypofunction in experimental animals and in neurodegenerative diseases (37).

Effects on Memory

Recent studies investigating the role of dopamine in working memory suggest that supranormal stimulation of D_1 receptors may contribute to the detrimental actions of do-

pamine on spatial working memory in the prefrontal cortex (8,51). One study directly tested this hypothesis by examining the effects of bilateral intra-PFC administration of the D_1 receptor agonist SKF 81297 (0.1 μg) into rats performing the spatial working memory task (T-maze). SKF 81297 produced a dose-related impairment in a working memory task. The impairment was reversed by pretreatment with SCH 23390 (0.01 mg/mL, i.p.). SCH 23390 by itself had no effect on performance cortex (8,51), demonstrating that supranormal D_1 receptor stimulation in the PFC is sufficient to impair PFC working function. These data are consistent with recent electrophysiological studies of D_1 receptor mechanisms affecting the PFC (75,76). However, recently Seamans et al. (58) have shown that local infusion of SCH 23390 (0.05–5 μg) into the prefrontal cortex blocked delayed-response task in rats on a radial-arm maze. Attentional performance was also tested using a five-choice serial reaction time task following intracortical (prefrontal) injection of SCH 23390 (0.3 μg), and selectively impaired the accuracy in high baseline correct responses (34). Conversely, intracortical administration of the D_1 receptor agonist SKF 38393 (0.6 μg) improved the accuracy, as well as the speed in making accurate responses, in the performance of the same task in rats that have low baseline correct responses. The latter improvement was antagonized by intracortical administration of SCH 23390 (1 μg) (34).

In Vivo Anticonvulsant Studies

The predominantly proconvulsant action of the nonselective antipsychotic drugs in humans first indicated that dopaminergic pathways might play a crucial physiological role in suppressing the genesis and dissemination of seizure activity in the brain (63). Since then, the generation of specific dopamine receptor antagonists and agonists has enabled much work into the involvement of the subtypes of dopamine receptor in epilepsy. Many models of epileptiform activity have been used to investigate the role of specific receptor subtypes in seizure activity. The commonly used species include rats, mice, gerbils, and rabbits, with little attention paid to the guinea pig. The methods of inducing seizures have included the use of genetically prone animals, kindling, electroshock, and the use of chemoconvulsants such as strychnine, soman, pentylenetetrazol (PTZ), and pilocarpine, among others. More recently, the advent of new technologies has made it possible to concomitantly study the behavioral, neurochemical, and electrophysiological effects of seizure activity *in vivo* by means of an assembly based upon the conventional microdialysis probe (13).

Behavioral Studies

The pilocarpine (muscarinic acetylcholine receptor agonist) model in rats and mice has been extensively used and is a reliable model for studying the processes of secondary generalized seizures initiated in the hippocampus. Previous studies have reported that the D_1 antagonist SCH 23390 (pretreatment with 0.1–0.3 mg/kg, i.p., in rats) dose-dependently abolished seizures evoked by a low dose of pilocarpine (200 mg/kg, i.p.) (10). However, motor seizures evoked by a higher dose of pilocarpine (600 mg/kg) were more difficult to suppress, and Turski et al. (67) reported that SCH 23390 was completely ineffective in this situation. However, Al-Tajir and Starr (2,4) showed that the intrastriatal injection of SCH 23390 (1 μg in each striatum) was capable of delaying the onset of forelimb myoclonus (repeated muscle contractions) and reduced the severity and lethality of motor (con-

vulsive) seizures evoked by pilocarpine (600 mg/kg, i.p.). This study also highlighted the previously held assumption that the dopamine receptor agonists/antagonists are more effective following their direct application to the brain. Burke et al. (16) showed that pretreatment of mice with SCH 23390 (0.8 mg/kg, i.p.), 60 min prior to pilocarpine 400 mg/kg, prevented fatalities and only 14.3% of animals exhibited convulsions, a proportion that was significantly lower than seen with pilocarpine treatment alone. More recently, pretreatment with SCH 23390 (0.5 mg/kg, i.p.) has been shown to prevent the onset of the predefined clinical signs associated with soman-evoked seizure activity (30.5 μg/kg, s.c.) in the guinea pig (Table 2), suggesting the involvement of the D_1 receptor subtype in the manifestation of these behaviors, probably through activation of the striatonigral GABAergic pathway (14). SCH 23390 has also afforded protection against pilocarpine-induced convulsions following the intrastriatal and intraaccumbal administration of the antagonist (2), but not following intrahippocampal administration (where it only delayed the onset of "limbic motor seizures") (5). These findings provide evidence of the involvement of the basal ganglia in the manifestation of motor convulsions evoked by cholinergic mechanisms. Stimulation of the D_2 receptor, following intranigral administration of the D_2 agonist LY 171555, did not protect against pilocarpine-induced convulsions (3). SCH 23390 at 0.3 and 0.5 mg/kg was, however, ineffective at preventing PTZ-evoked seizures in mice.

Neurochemical Studies

In the soman model (30.5 μg/kg, s.c.) of seizure activity in the guinea pig, pretreatment of SCH 23390 (0.5 mg/kg, i.p.) resulted in changes to the striatal neurochemistry. Inhibition of the dopamine D_1 receptor evoked a relative decrease in striatal extracellular dopamine and its metabolites (HVA and DOPAC) compared with that seen with soman alone, in which the animal had electrographic and behavioral seizures (Fig. 2). This suggests that the level of striatal extracellular dopamine is strongly influenced by the seizure activity evoked by the chemoconvulsant soman. Also in the same study, a relative decrease was observed in the concentration of striatal extracellular acetylcholine (ACh), suggesting that the D_1 heteroreceptors located on the striatal intrinsic cholinergic neurons are capable of modulating the release of ACh in an excitatory manner (14). In guinea pigs

TABLE 2. Time to onset (min; mean ± S.E.M., n = 5) of pre-defined clinical signs, following the administration of soman (30.5 μg/kg). None of these clinical signs were observed in animals pre-treated with SCH 23390 (0.5 mg/kg)

Clinical sign	Time to onset (min)
Chewing	12 ± 1
Haunched posture	10 ± 3
Splayed hind limbs	27 ± 4
Circling	28 ± 4
Tremor	32 ± 4
Writhing, ataxia	56 ± 11
Myoclonic convulsions	53 ± 11
Vocalization	79 ± 9

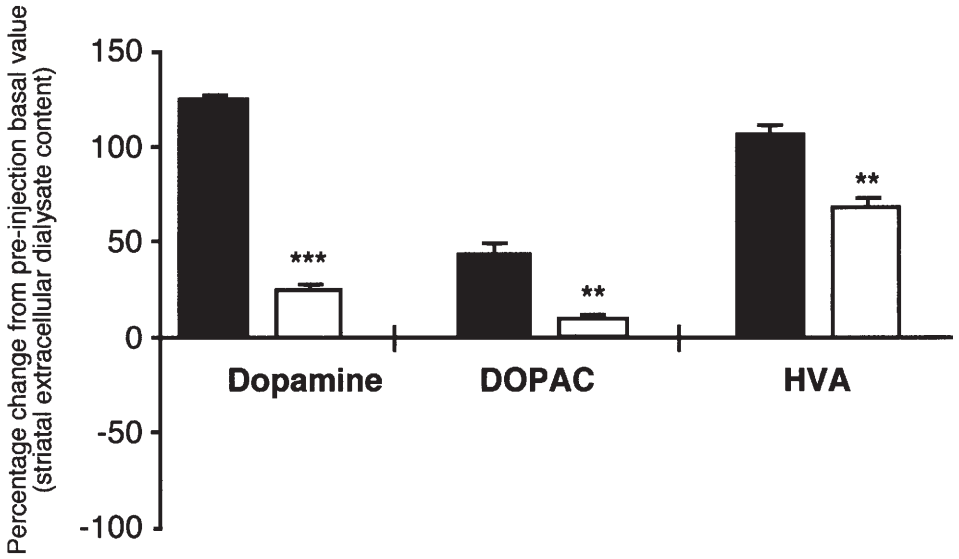

Fig. 2. Evoked changes "total effect" in the striatal extracellular dialysate content of dopamine, DOPAC and HVA following administration of soman (30.5 μg/kg; solid bars) and SCH 23390 (0.5 μg/kg) + soman (open bars), in the guinea pig. Results are expressed as a percent of the respective baseline values (mean ± S.E.M., $n = 5$). $^{**}P < 0.01$; $^{***}P < 0.001$, soman vs. SCH 23390 + soman; two-tailed Mann–Whitney *U*-test.

treated with the excitotoxin, kainic acid (12 mg/kg), and pretreated with SCH 23390 (0.5 mg/kg, i.p.) there was incomplete attenuation of seizure activity; this was accompanied by a significant relative decrease in dopamine, but not its metabolites (Fig. 3). A decrease was observed also in the striatal extracellular aspartate and glutamate levels. However, an increase in GABA levels was observed (Fig. 4) (15). The increase in dopamine, compared with that observed with kainic acid alone, could be a result of the activation of kainic acid release-enhancing heteroreceptors, located on the terminals of the nigrostriatal dopaminergic neurons (47,48). The lack of change in the metabolites DOPAC and HVA suggests no increase in the metabolism of dopamine. The decrease in the striatal extracellular concentration of excitatory amino acid neurotransmitters aspartate and glutamate, compared with that seen with kainic acid alone, suggests a decrease in the activation of the corticostriatal glutamatergic fibers, presumably due to a decrease in the activation of the cortex (seen in the EEG). The increase in GABA is more difficult to explain, since the inhibition of the dopamine D_1 heteroreceptors located on the striatal GABAergic interneurons would usually result in a decrease in the release of GABA (8,51). Therefore, other receptors or pathways may be implicated.

Electrophysiological Studies

The capability of the D_1 antagonist SCH 23390 to prevent cortical electrographic (ECoG) paroxysmal activity has been observed in the pilocarpine model (200 mg/kg, i.p.) of epileptiform activity in rats (10). This specific activity of the dopamine D_1 receptor was also supported by results in the same study, which showed that systemic administration of the D_1 agonist SKF 38393 exacerbated the seizure activity relative to that seen with higher

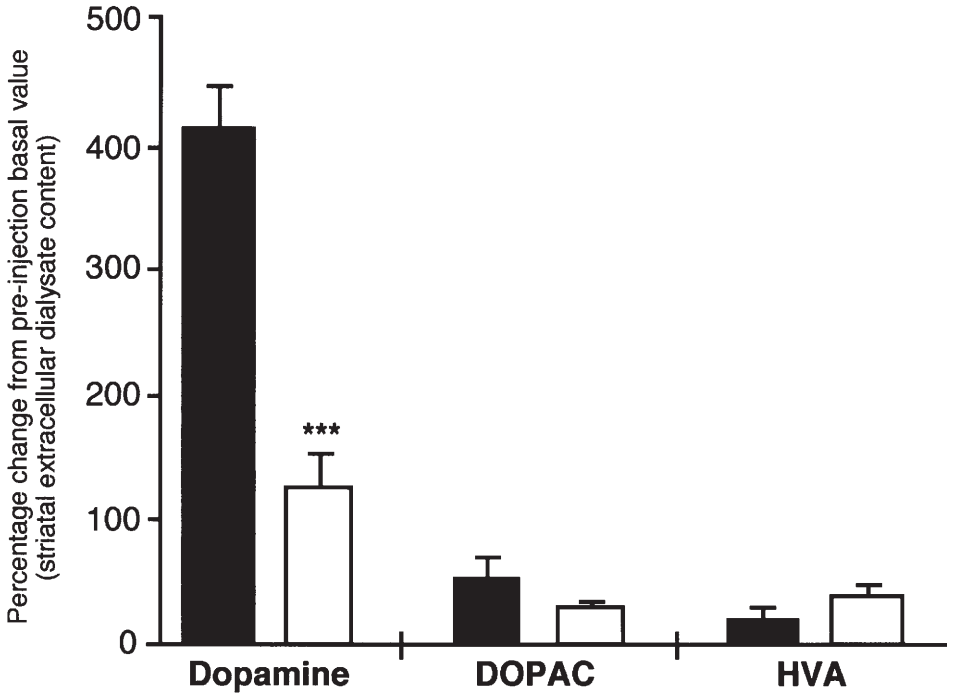

Fig. 3. Evoked changes "total effect" in the striatal extracellular dialysate content of dopamine, DOPAC and HVA following administration of kainic acid (12 mg/kg; solid bars) and SCH 23390 (0.5 mg/kg) + kainic acid (open bars), in the guinea pig. Results are expressed as a percent of the respective baseline values (mean ± S.E.M., $n = 5$). ***$P < 0.001$, kainic acid vs. SCH 23390 + kainic acid; two-tailed Mann–Whitney *U*-test.

doses of the chemoconvulsant. In the soman model (30.5 μg/kg, s.c.) of seizure activity in the guinea pig, pretreatment with SCH 23390 (0.5 mg/kg, i.p.) was capable of preventing the onset of electrographic seizure activity in both the striatum (EStG) and the cortex. This resulted in a significant decrease in the EEG power compared with that seen with soman alone (Fig. 5), which was at a similar level to that seen prior to the injection of the chemoconvulsant. Conversely, following pretreatment with the D_2 receptor antagonist sulpiride (30 mg/kg), there was an earlier onset of an EEG-defined *status epilepticus* and an increase in the power of the EEG but not in behavioral paroxysmal activity (14). With kainic acid (12 mg/kg, i.p.) and pretreatment with SCH 23390 (0.5 mg/kg, i.p.) the dopamine antagonist did not totally ameliorate the paroxysmal activity but reduced the severity of the seizure activity in terms of the power of the EEG (Fig. 6), and more interictal periods were observed (15). The D_2 receptor agonist LY 171555 (0.5 mg/kg) similarly depressed pilocarpine-induced seizures when administered subcutaneously (4). These studies indicate that the two dopamine receptor subtypes, D_1 and D_2, exert opposing roles in the generation of electrographic seizure activity. While it may be an overgeneralization to characterize D_1 and D_2 receptors as mediating pro- and anticonvulsive roles, empirical evidence certainly characterizes both a detrimental and beneficial function in man.

One caveat that has come from these studies is the importance of distinguishing electrographic and behavioral seizure activity as the clinical signs often used to determine

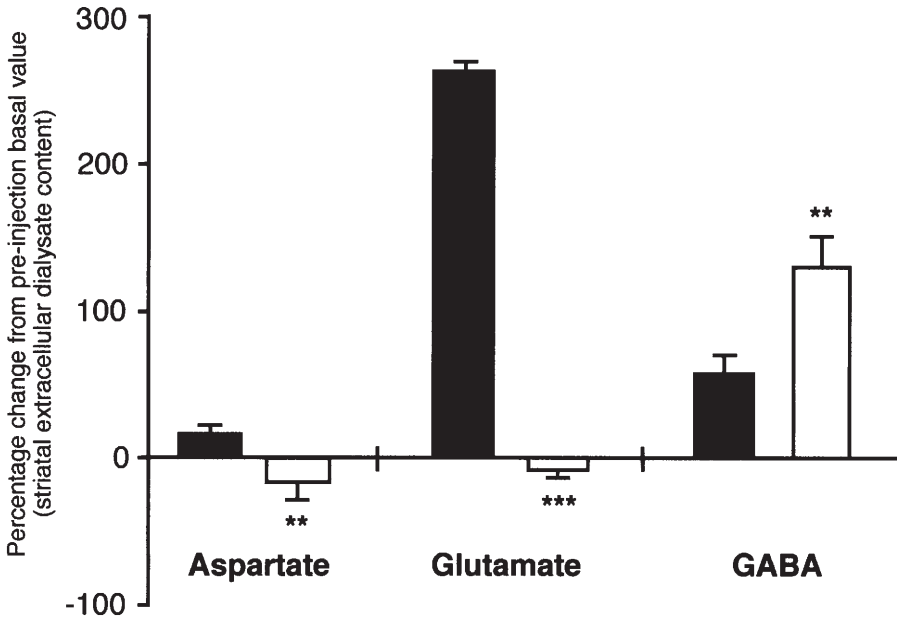

Fig. 4. Evoked changes "total effect" in the striatal extracellular dialysate content of aspartate, glutamate and GABA following administration of kainic acid (12 mg/kg; solid bars) and SCH 23390 (0.5 mg/kg) + kainic acid (open bars), in the guinea pig. Results are expressed as a percent of the respective baseline values (mean ± S.E.M., $n = 5$). $^{**}P < 0.01$; $^{***}P < 0.001$, kainic acid vs. SCH 23390 + kainic acid; two-tailed Mann–Whitney *U*-test.

stages of seizure activity, e.g., intermittent and status epilepticus, have been shown in certain cases not to relate to electrographical activity (13,18).

Studies in Other Diseases of the Central Nervous System

Parkinson's and Huntington's diseases

Blockade of the dopamine D_1 receptor subtype with a single dose of SCH 23390 increases the activity of aromatic L-amino acid decarboxylase (AAAD), which converts L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine. When L-DOPA is administered to rats after pretreatment with SCH 23390 there is a significant increase in the formation of DOPAC and dopamine turnover in striatum and midbrain compared with L-DOPA alone, suggesting further enhancement of dopamine metabolism. These studies suggest that it may be possible to enhance the conversion of L-DOPA to dopamine in Parkinson's disease patients by administering substances that augment brain AAAD, such as SCH 23390 (52). In Huntington's disease, studies with [^{11}C]SCH 23390 and [^{11}C]raclopride have shown that positron emission topography (PET) measures of human striatal D_1 and D_2 dopamine binding, respectively, can be used to identify asymptomatic Huntington's disease mutation carriers who are actively progressing and who would, thus, be suitable for putative neuroprotective therapies. Measures of disease progression rates in Huntington's disease patients and asymptomatic mutation carriers using these radiolabeled ligands will be of critical importance in future trials of experimental restorative treatments (7,33,72).

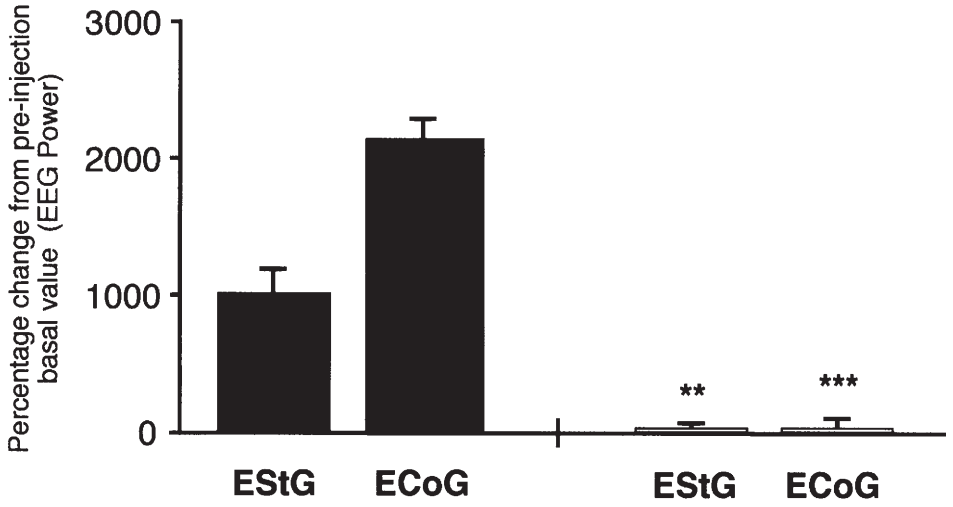

Fig. 5. Evoked changes "total effect" in the EEG power of both striatal and cortical EEG following administration of soman (30.5 μg/kg; solid bars) and SCH 23390 (0.5 mg/kg) + soman (open bars), in the guinea pig. Results are expressed as a percent of the respective baseline values (mean ± SEM, $n = 5$). $^{**}P < 0.01$; $^{***}P < 0.001$, soman vs. SCH 23390 + soman; two-tailed Mann–Whitney *U*-test.

Psychosis

The role of D_1 receptors in schizophrenia is tentative (23,69) but in preclinical trials SCH 23390 has been reported to have an antipsychotic action in schizophrenic patients, without inducing extrapyramidal side effects, such as spasms, restlessness, and pseudoparkinsonism (24,25). Hietala et al. (39) have, however, concluded from the majority of the available data that SCH 233390 does not share the profile of atypical neuroleptics. Farde (30) showed that administration of SCH 23390 to four healthy subjects at doses of 310–810 μg, i.v., induced akathisia, the syndrome of motor restlessness, at the three highest doses. However, akathisia is a transient effect (32). As with the prototypic atypical antipsychotic clozapine, that is routinely used in the treatment of schizophrenia, SCH 23390 may be exerting its direct/indirect action with nondopaminergic systems, such as 5-HT. Unfortunately, based on the current literature on the relevance of the D_1 receptor to higher cognition, it would be contradictory to block D_1 receptors in schizophrenia to relieve their cognitive deficits and associated psychotic symptoms. Indeed, recent clinical trials of the more selective D_1 receptor antagonist SCH 39166 revealed that it is incapable of improving schizophrenic symptoms (44). Moreover, recent electrophysiological findings of a D_1 potentiation of NMDA receptor functions in the PFC, striatum, and hippocampus may further illustrate the role of the D_1 receptor in improving cognition, as well as in inducing seizures as a result of the overstimulation of NMDA receptor (19,20,58).

Other idiopathic psychotic disorders in which dopamine receptors have been implicated include paranoia, mania, Tourette's syndrome, major depression, childhood attention–hyperactivity disorder and substance abuse/addiction.

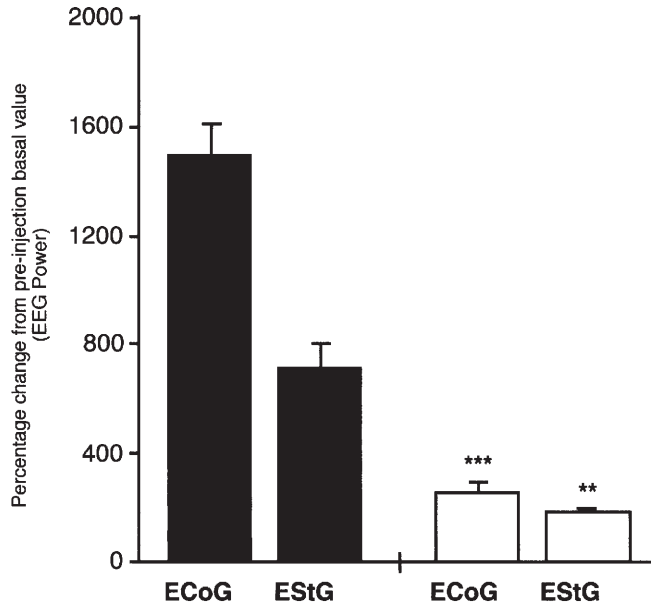

Fig. 6. Evoked changes "total effect" in the EEG power of both striatal and cortical EEG following administration of kainic acid (12 mg/kg; solid bars) and SCH 23390 (0.5 mg/kg) + kainic acid (open bars), in the guinea pig. Results are expressed as a percent of the respective baseline values (mean ± S.E.M., $n = 5$). $^{**}P < 0.01$; $^{***}P < 0.001$, kainic acid vs. SCH 23390 + kainic acid; two-tailed Mann–Whitney *U*-test.

CONCLUSIONS

The anticonvulsant properties of SCH 23390 highlight the importance of the D_1 dopaminergic mechanisms in facilitating the initiation and spread of generalized seizures and that inhibition of the release-enhancing dopamine D_1 receptor located on the terminals of the GABAergic striatonigral neurons possibly attenuates seizure activity. This evidence is further supported by results from the rat showing that the D_1 agonist SKF 38393 (30 mg/kg, i.p.) is proconvulsant in a pilocarpine model of epileptiform activity by virtue of its activity at dopamine D_1 receptors (4,2,10). It has also been concluded that the normal synergistic balance of the dopamine D_1 and D_2 receptor subtype activity confers resistance to seizure-promoting stimuli (2). Further investigation with the selective antagonist SCH 23390, utilizing techniques to monitor neurochemistry and electrophysiology should yield a better mechanistic picture of the role of these receptors in many paradigms.

While there is no immediate prospect of developing D_1 receptor antagonists, specifically SCH 23390, as clinically useful antiepileptics, there is a growing awareness that seizures might be precipitated as a consequence of the treatment of other neurological disorders, e.g., the use of D_1 agonists in Parkinson's disease. Unfortunately, the pharmacokinetic properties of the drug and the results of previous animal studies (70), which indicate that the D_1 receptor antagonists can induce stereotypical and atypical behaviors, make SCH 23390 somewhat unlikely as a possible therapy. However, a better understanding of the involvement of striatal dopaminergic receptor subtypes, with respect to seizure ac-

tivity, has implications for these receptors as a possible target for the prevention or amelioration of epileptic seizures.

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